UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,721	02/12/2001	H. Michael Shepard	126745200402	5394

23639 7590 09/27/2004

BINGHAM, MCCUTCHEN LLP
THREE EMBARCADERO, SUITE 1800
SAN FRANCISCO, CA 94111-4067

EXAMINER	
CRANE, LAWRENCE E	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 09/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,721	SHEPARD ET AL.	
	Examiner	Art Unit	
	L. E. Crane	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06/07/04 (amdt & IDS)*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-79,81-84 and 86-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-79,81-84 and 86-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/07/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims **80 and 85** have been cancelled, claims **56-58, 62, 76, 81, 84 and 86** have been amended, the disclosure has not been amended, and no new claims have been added as per the amendment filed November 10, 2003. One additional Information Disclosure Statement (IDS) filed June 7, 2004 has been received along with all cited references and made of record.

Examiner notes applicant has given notice of the filing of a related application identified as US Application No. **10/048,033**. The IFW file for this application is incomplete and is missing in particular the claims and the disclosure. Therefore, in order to avoid the need to make a new grounds of rejection in the future, a rejection over "the claims" in this new application has been made. Applicant is respectfully requested to supply a separate courtesy copy of the claims in the **'033** application to examiner

Claims **56-79, 81-84 and 86-89** remain in the case.

Claims **56 and 57** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims **56 and 57** are directed to methods of inhibiting and treating wherein the particular disease to be treated has not been specified, the particular active ingredients have not been defined, and the host has not been defined by the functional terms "phosphoramidatyl prodrug" and "hyperproliferative neoplastic cell(s)." These terms are the equivalent of laundry list disclosures which fail to meet the written description requirement because each, taken individually or taken together, "... would not 'reasonably lead' those skilled in the art to any particular species." (MPEP §2163 (A) at p. 2100-160, column 2, making reference to *In re Rushig*, 379 F2d 990, 995 (CCPA 1967).

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

Applicant's amendment is noted but is not deemed to overcome the instant grounds of rejection.

Applicant argues that the Office argues without factual basis. Applicant is referred to newly cited references **SA** and **TA** and to the following remarks.

Applicant is referred to the newly cited PTO-892 references **SA** (Stedman's Medical Dictionary) and **TA** (Merck Manual) wherein the vast subject matter area of neoplastic disease conditions and the treatment(s) thereof are briefly summarized. In light of the minimal nature of the instant disclosure examiner is presently unable to agree with applicant's claims which represent an extrapolation based on only the single instant example of antineoplastic disease treatment to the encompass the generic class of all neoplastic disease conditions. Applicant's reference to other compounds and two test regimens directed to treating specific colon and breast cancers in other references is noted but does not overcome the instant grounds. Applicant is referred to Applicant is referred to *Ex parte Balzarini,* 21 USPQ 2d 1892 (Bd Pat App & Inter, 1992) for guidance regarding the enhanced enablement needed to support claims directed to methods of treating HIV and which accurately reflects current PTO policy with regard to medicinal methods of treating generally. A much more comprehensive showing of efficacy against a broad range of different cancers *in vitro* or *in vivo* has not been provided.

Claims **56-61, 81-84 and 86-89** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in In re Wands (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims as defined by the terms "hyperproliferative neoplastic cell(s)" is excessively broad because said term reads on multiple different disease conditions including all varieties of neoplasms (cancers cells). Only in claim **89** is the term limited to specific neoplastic diseases.

B. The nature of the invention as described in the specific examples is limited to a showing that a single compound, a phosphoramidated derivative of 5-bromovinylated 2'-deoxyuridine nucleoside is much more effective that the non-phosphoramidated BVDU base

compound in treating certain specific neoplastic diseases, human breast carcinoma and human colon carcinoma in particular.

C. The state of the prior art; the extensive prior art of record, as presently understood and reviewed, does not anticipate or render obvious the treatment of carcinomas with a phosphoramidated BVDU.

D. The level of one of ordinary skill is defined by the need to understand organic synthesis, and the testing of compounds in *in vitro* cell culture.

E. The level of predictability in the art is low because only two closely related neoplastic disease conditions have been shown to be effectively inhibited by a phosphoramidated BVDU compound.

F. The amount of direction provided by the inventor is limited to showing how to make and administer a single phosphoramidated BVDU compound to cause inhibition of two closely related neoplastic disease conditions.

G. The existence of working examples is limited to a single compound administered to cells in in vitro culture infected by two closely related carcinomas.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure would be excessive because the disclosure does not described how to effectively treat anything other than carcinoma in humans breast and colon tissue.

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

Applicant is referred to the response following the rejection above.

Claims **62-79** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in In re Wands (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims is very large particularly in view of terms found in claim **62** wherein a large array of compounds is disclosed, only one of which is actually prepared and shown to be thymidylate-synthase activatable in a testing protocol.

B. The nature of the invention is compounds and methods of treating neoplastic disease conditions and a related protocol for determination of the anti-neoplastic activity of test compounds

C. The state of the prior art is not well advanced as revealed by the absence of an art rejection.

D. The level of one of ordinary skill is high, a knowledge of chemical synthesis, biochemistry, enzymology and pharmacology being required to carry out all elements of the instant claimed invention.

E. The level of predictability in the art is low, because of the very small amount of testing data.

F. The amount of direction provided by the inventor is very low because only a single compound, the 5'-phosphoramidate ester of 5-bromovinyluridine has been synthesized and shown to have the anti-neoplastic activity.

G. The existence of working examples is very limited: only a single compound has been prepared and shown to have anti-neoplastic activity; and

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure would be excessive, particularly because only a single compound has been prepared and its preparation has been shown to be very sensitive to reaction conditions, a showing that provides no basis for extrapolation to other compounds with different toxophoric substituents as provided for by the instant claims.

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

Applicant is referred to the response following the first rejection under 35 U.S.C. §112, first paragraph. In addition, applicant is respectfully requested to note that all of the instant noted claims are either generic or subgeneric and thereby each encompasses extremely large number of compounds as a direct consequence of applicant's reliance of functional language in claim **62**.

Claims **56-59, 61-63, 65, 72, 81-84 and 86-87** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims **56 and 57** the term "a 5'-phosphoryl or phosphoramidatyl prodrug of a 5-substituted pyrimidine nucleoside or nucleotide, a derivative or a metabolite thereof" fails to completely define the structural metes and bounds of the included terms "phosphoramidatyl," "5-substituted pyrimidine nucleoside or nucleotide," and "a derivative or a metabolite thereof." In light of the initial requirement of a "5'-phosphoryl or phosphoramidatyl" substituent it is also unclear where the additional "phosphate" group(s) are located as required by the included term "nucleotide." See also claim **58** wherein the terms "prodrug," "derivative," and "metabolite" also appear at lines 1-2.

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

Applicant argues that the noted terms are "well known in the art" and "employ language conventionally used in the art to which the invention pertains," but these arguments fail to effectively address the rejection. Applicant is respectfully requested to note that language conventional in the art in the instant case remains inadequate to meet the requirement of the statute; the metes and bounds of the claimed subject matter remain inadequately defined.

In claim **57** at line 1, the term, "hyperproliferative neoplastic cells, " is indefinite for failure to specify the particular disease being referred to; is it cancer and if so which cancer or cancers? See also claims **56, 58, 81-84, 86 and 87**. The term "pathological hyperproliferative cell" is no better because it also fails to define the particular disease(s) to be treated.

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

Applicant is referred to newly cited PTO-892 reference **SA** and **TA** wherein very extensive but by no means comprehensive lists are found of neoplastic disease conditions within the definitions of the terms "neoplasia," "neoplasm," and "cancer." The amendment of the previous term is noted, but in light of the definitions noted, is not deemed to overcome the rejection of record in light of the large number of "neoplastic" diseases with widely varying etiologies.

In claim **58** the terms "an electrophilic leaving group" (line 4), "a phosphoryl or phosphoramidatyl" (line 6), and "masked phosphoryl," (line 9) are incomplete for failure to completely specify the metes and bounds of the chemical structures being claimed.

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

Applicant has noted this grounds of rejection but has not specifically responded thereto. Applicant is reminded that words alone fail to adequately define the chemical structures being claimed.

In claim **58** the terms "sugar," "thio sugar," "carbocyclic," "acyclic analogs and derivatives of a sugar," "a thio-sugar or a carbocyclic," "derivatives," "analogs" are indefinite for failure to provide the structural details to the chemical species being referred to. In addition, the term "carbocyclic" is unnecessarily repeated and also is not further provided with an upper size limit; the terms "sugar" and "thiosugar" are compounds (-- sugar group --?); and, the terms "analogs" and "derivatives" are open ended (no metes and bounds or other limits on the definition).

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

Applicant is referred to the responses to previous rejections under 35 U.S.C. §112, second paragraph.

Claim **59** is indefinite for failure to provide the structural details for the chemical species ("masked phosphoryl moiety" and "phosphoramidatyl moiety") being referred to.

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

Applicant is referred to the responses to previous rejections under 35 U.S.C. §112, second paragraph.

In claim **62** at lines 10-11, the term "aromatic hydrocarbyl" is incomplete because said terms both lack an upper size limit and therefore render the instant compound indefinite for failure to provide adequately defined structural metes and bounds. Also, the term "heteroaromatic" is incompletely defined for failure to define the identity or limits on the proportion of the heteroatom or heteroatoms present.

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

The above groups of rejection have been narrowed in response to applicant's clarifying amendments. However, said amendments fail to entirely address the issues remaining, issues which have not been directly addressed in applicant's response. Therefore, the above rejection has been maintained.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F. 2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir 1985); and *In re Goodman,* 29 USPQ 2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. §1.78(d).

Effective January 1, 1994, a registered attorney or agent or record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

Claims **56-61, 81-84 and 86-89** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim **1-12** of U. S. Patent No. **6,495,553**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

Applicant has acknowledged but has deferred response to this grounds of rejection.

Claims **62-79** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **36-39** of U. S. Patent No. **6,339,151**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

Applicant has acknowledged but has deferred response to this grounds of rejection.

Claims **56-79, 81-84 and 86-89** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-7** of U. S. Patent No. **6,245,750**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

Applicant has acknowledged but has deferred response to this grounds of rejection.

Claims **56-79, 81-84 and 86-89** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-30** of co-pending Application No. **10/119,927**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds and the methods of treatment are overlapping with the instant claimed subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

Applicant has acknowledged but has deferred response to this grounds of rejection.

Claims **56-61 and 81-84 and 86-89** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-22** of co-pending Application No. **10/051,320** (for the PG PUBS version, see PTO-892 ref. **P3**). Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds and the methods of treatment are overlapping with the instant claimed subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

Applicant has acknowledged but has deferred response to this grounds of rejection.

Claims **62-79** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1 and 53-83** of co-pending Application No. **10/681,418**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

Applicant has acknowledged but has deferred response to this grounds of rejection.

Claims **56-79, 81-84 and 86-89** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-10** of U. S. Patent No. **6,683,061** (PTO-892 ref. **AB**). Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds and the methods of treatment are overlapping with the instant claimed subject matter.

Applicant's arguments filed June 7, 2004 have been fully considered but they are not persuasive.

Applicant has acknowledged but has deferred response to this grounds of rejection.

Claims **56-79, 81-84 and 86-89** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over **the pending claims** of co-pending US Application No. **10/048,033**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds and the methods of treatment are overlapping with the instant claimed subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments with respect to claims **56-79, 81-84 and 86-89** have been considered but are deemed to be moot in view of the new grounds of rejection. This new grounds of rejection was necessitated by applicant's filing of a new application.

Claims **56-79, 81-84 and 86-89** of this application conflict with claims ***1-30*** of co-pending US Application No. **10/119,927** claims ***1-22*** of co-pending US Application No. **10/051,320**, claims ***1 and 53-83*** of co-pending US Application No. **10/681,418**, and of **the pending claims** of co-pending US Application **10/048,033**. 37 C.F.R. §1.78(b) provides that

when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP §822.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. §1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. §1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

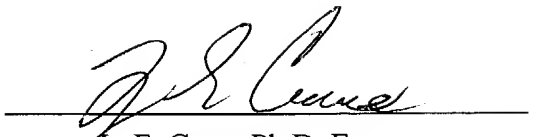
Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX directly to Examiner's computer is 571-273-0651. The telephone number for submission of an official FAX to the USPTO is **(703) 872-9306**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at **571-272-0661**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec
09/13/2004



L. E. Crane Ph.D. Esq.
Patent Examiner
Technology Center 1600